Arkema Inc.

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Test Plan for:

Tetradecyloxirane [CASRN 7320-27-8]

Prepared for

U.S. Environmental Protection Agency
HPV Challenge Program
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1 EXECUTIVE SUMMARY

IN 2005 Arkema Inc. volunteered to sponsor tetradecyloxirane (CAS#7320-38-7) also know as 1,2-epoxyhexadecane, in the US EPA High Production Volume (HPV) Challenge Program. This material was previously considered an orphan under the HPV program.

This report and test plan covers the physical property; environmental fate processes; and the ecological, mammalian, and genetic toxicity endpoints for tetradecyloxirane as appropriate for a chemical intermediate with controlled transport.

Existing Data

Data on physical properties, environmental fate, ecotoxicity, and mammalian and genetic toxicity were collected from available reports, published literature, and various standard compilations of physical property data. The collected data were reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier.

Ecotoxicity, mammalian toxicity, and genetic toxicity data were scored using the Klimisch et al. (1977) scoring system to assess data reliability. Data with scores of 1 or 2 were considered reliable and sufficient to assess an endpoint without supplementary data. Studies rated 4 were considered supplementary. Robust summaries were prepared for available reliable studies and relevant supplementary data and were entered into the IUCLID dossier.

Tetradecyloxirane is a metabolite of 1-hexadecene, which has been evaluated in the HPV Challenge Program as part of the as part of the higher olefins category. Some supplementary data for tetradecyloxicrane includes the assessment of 1-hexadecene.

Tetradecyloxirane is an isolated intermediate with controlled transport to a limited number second parties that use the chemical in a controlled way as an intermediate with a well-known technology. Repeat dose data up to 2 year studies in two species are available.

The proposed test plan is summarized in Table 1.

Table 1. Proposed Tests for Tetradecyloxirane

Endpoint	Testing Proposed	Rationale
Melting point	No	Adequate existing information
Boiling point	No	Adequate existing information
Density	No	Adequate existing information
Partition coefficient	No	Adequate existing information
Water solubility	No	Estimated using EPIWIN v3.12
Photodegradation	No	Estimated using EPIWIN v3.12
Transport between environmental compartments	No	Estimated using EPIWIN v3.12
Stability in water	Yes	
Biodegradation	No	Adequate existing information
Acute fish	No	Adequate existing information
Acute Daphnia	No	Adequate existing information
Toxicity to algae	Yes	
Acute toxicity	No	Adequate existing information
Repeated dose toxicity	No	Adequate existing information
Reproductive toxicity	No	Adequate existing information
Developmental toxicity	No	Adequate existing information
Genetic toxicity	No	Adequate existing information

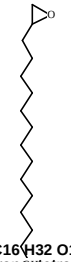
1.1 TEST SUBSTANCE

1.2 GENERAL SUBSTANCE INFORMATION

This material is used as a chemical intermediate with controlled transport. It is produced at a single location and shipped to a small number of second party users/locations where it is converted during processing to produce lubricants, surfactants, and additives for functional fluids for machinery, vehicles, and equipment. Any exposure potential would be limited to an industrial occupational setting. Tetradecyloxirane is an irritating material and a sensitizer.

Precautions are taken in manufacturing and processing to prevent contact. It is consumed and converted during processing. The products produced from the tetradecyloxirane are further diluted and used in formulations. There is no to very low potential for exposure to the tetradecyloxirane outside industrial occupational settings.

Table 2. General Substance Information

Compound	CAS No.	Molecular Formula	Molecular Weight (g/mol)	Estimated Purity of Named Substance	Structural Diagram
Tetradecyloxirane	7320-37-8	$C_{16}H_{32}O$	240.42	98%	 MolWt: 240.43 C16H32 O1 007320-37-8 Oxirane, tetradecyl-

1.3 REACTIVITY

Epoxides contain 3 membered carbon-carbon-oxygen rings which are reactive, due to the strain on the ring. Nucleophilic attack breaks a carbon-oxygen bond, opening the ring and relieving the strain. Generally, the result is the formation of a substituted alcohol; if the nucleophile is water, then diols or glycols are formed. Weak nucleophiles such as water require acid catalysts for the reaction to occur. Under acidic conditions, the nucleophile preferentially attacks the more substituted carbon in the ring, resulting in the formation of the less substituted alcohol. Under basic conditions, the nucleophile attacks the least hindered carbon in the ring and results in the formation of the more substituted alcohol. In living systems the enzyme epoxide hydrolase converts epoxides to trans-dihydrodiols. Based on these properties, this high molecular weight epoxide is stable under normal storage and handling conditions. Contact with acids, bases, or oxidizers can result in a low energy release.

1.4 DISCUSSION OF THE ADEQUACY OF THE EXISTING DATA

Arkema has reviewed the existing data set and feels that the existing data are adequate to characterize several of the aquatic and health effects of tetradecyloxirane for the purposes of the EPA HPV Challenge Program. Table 1 indicates where additional data are proposed to be developed.

2 PHYSICAL PROPERTY DATA

For tetradecyloxirane, data on physical properties were collected from reports, published literature, and various standard compilations of physical property data. The collected data were

reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier. Existing physical property data are summarized in Table 3 below.

Table 3. Physical Property Data for Tetradecyloxirane

Endpoint	Value	Source(s)
Melting Point	21°C(1)	The Dictionary of Substances and Their Effects (DOSE, 3rd Electronic Edition) 2005
Boiling Point	270 - 275 °C	Safety and Toxicity Data prepared for 1,2-epoxyhexadecane by Tracor Jitco July 26, 1978.
Density (g/cm^3)	0.85 @ 20 °C	The Dictionary of Substances and Their Effects (DOSE, 3rd Electronic Edition) 2005
Vapor Pressure	ca. 0.00285 hPa @ 25 °C	EPISuite v3.12 (MPBPWIN V. 1.41)
Partition Coefficient (log P_{ow})	ca. 6.76 @ 25 °C	EPISuite v3.12 (KOWWIN v1.67)
Water solubility	0.045 mg/L @ 25 °C	EPISuite v3.12 (WSKOW v1.41)
	0.0006 mg/L	Wood, 1982

Existing physical property data are considered adequate; therefore, no additional testing is proposed.

3 ENVIRONMENTAL FATE DATA

3.1 PHOTODEGRADATION

The Atmospheric Oxidation Program for Microsoft Windows (EPISuite v 3.12, AOPWIN v1.91) was used to estimate the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. These rate constants were used to calculate atmospheric half-lives based upon average atmospheric concentrations of hydroxyl radicals and ozone. The results are presented below and indicate that there is a moderate reaction rate and it will not be persistent in air.

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant =	18.7709 E-12 cm3/molecule-sec
Half-Life =	0.570 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =	6.838 Hrs

3.2 ENVIRONMENTAL TRANSPORT AND DISTRIBUTION (FUGACITY)

Fugacity modeling was performed using EPISuite v3.12. The results are listed below:

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.531	13.7	1000
Water	4.42	360	1000

Soil	31.2	720	1000
Sediment	63.8	3.24e+003	0

Persistence Time: 1.11e+003 hr

Based on this model the material is expected to partition primarily to soil and sediment.

3.3 BIODEGRADATION

Aerobic degradation was 26% after 20 days, so the material is inherently biodegradable. No testing is proposed. (Waggy, G.T., 1992).

3.4 STABILITY IN WATER (HYDROLYSIS)

There are no rate data related to the stability in water. Epoxides have the potential to undergo hydrolysis. Experience has shown that tetradecyloxirane is stable in water at neutral pH and room temperature, but will hydrolyze to form the glycol in acid solutions. Hydrolysis testing is proposed.

4 ECOTOXICITY DATA

Ecotoxicity data were collected from reports and published literature. The collected data were reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier.

4.1 ACUTE TOXICITY TO FISH

Data in the literature indicates that the LC50 is greater than the limit of solubility. (Deneer et al., 1988) Modeling makes the same prediction. No further testing is proposed.

4.2 ACUTE TOXICITY, AQUATIC INVERTEBRATES (DAPHNIA)

The EC50 for Daphnia magna is reported to be 1.25 mg/l. These data are adequate. No further testing is proposed. (Waggy, GT, 1992)

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

No data on the toxicity to algae are available. Testing for algal toxicity is proposed.

5 MAMMALIAN TOXICITY

Based on animal studies, tetradecyloxirane had low acute oral and dermal toxicity, was slightly irritating to eyes, severely irritating to skin, and caused skin sensitization. It was not mutagenic when tested in bacteria, but elicited chromosomal effects to some types of cells in culture, and was negative in others. Histopathological findings in subchronic dermal studies (13 week duration) were identified in the skin but not in tissues remote from the site of application. Long term dermal exposure resulted in the development of skin tumors in mice but not rats.

5.1 ACUTE TOXICITY

The rat oral LD50 is greater than 5000 mg/kg. The rat dermal LD50 is greater than 2000 mg/kg. Clinical signs were noted in both studies during the observation period but no significant findings were noted at gross necropsy. (Springborn, 1996, 1996a) No further testing is proposed.

5.2 IRRITATION AND SENSITIZATION

Results of animal studies showed moderate (Myers and Christopher, 1992) to severe skin irritation (Springborn, 1996b). Some signs of irritation persisted up to the observation recorded on day 10 after dosing. All animals had recovered by the study termination at day 14. Minor transient conjunctival irritation was noted after application of 0.1 ml to rabbit eyes. All animals recovered completely by day 7. (Myers and Christopher, 1992; Springborn, 1996c)

Tetradecyloxirane was tested to assess the dermal sensitization potential (delayed contact hypersensitivity) in Hartley-derived albino guinea pigs when administered by multiple topical applications. Based on the results of this study, this material is considered to be a contact sensitizer in guinea pigs. (Springborn, 1996d)

5.3 REPEATED DOSE TOXICITY

Although the final reports of the NTP studies have never been published, the data are available in the archive. The information below was extracted from the records in the archive. (NTP Unpublished Study C55538)

Subchronic studies:

NTP conducted a 13 week skin painting study in rats as a dose range finding study prior to conducting a chronic study. Ten animals per sex per dose were administered test material 5 days per week for 13 weeks. The applied doses were 0, 62.5,125, 250, 500, and 1000 mg/kg at concentrations of 0, 3.75, 7.5, 15. 30, 60% in acetone.

Clinical observations were limited to irritation at the lower doses. At 500 mg/kg, during weeks 3 - 8, exfoliation of stratum corneum and alopecia were reported. Some females were thin. At 1000 mg/kg, during weeks 1 - 3, rough coats and slight erythema were observed; during weeks 4 - 13, exfoliation of the stratum corneum was also reported. During weeks 5 - 13, dark urine, emaciation (primarily in females), alopecia, and sores in treated area were reported.

There were compound related lesions observed in this study. These lesions the skin (site of application) and were manifested in a variety of changes. These changes consisted of

hyperkeratosis, parakeratosis, acanthosis, necrosis of cells, and necrosis with varying degrees of inflammation. In more severe cases, mostly high dose and mid dose animals, there was ulceration of the skin accompanied with acute and chronic inflammation. In one case, high dose male, there were pyogenic granulomas deep in the dermis and muscle.

Microscopic findings were limited to the skin and site of application. Deep dermal abscesses, focal ulceration, inflammation were reported.

A similar skin painting study was conducted in mice. Applied doses were 0, 62.5, 125, 250, 500, and 1000 mg/kg using test concentrations of 0, 0.9, 1.875, 3.75, 7.5, and 15%.

Reduced body weights were observed in males at doses > 250 mg/kg, beginning in the fourth week , but the body weights recovered to near controls for all doses by end of the study. Mean body weights of females varied too widely for any meaningful relationship to treatment.

Clinical observations, males: Males in all dose groups had sores on their backs likely due to fighting. Dose related signs of skin irritation were also noted. At 250 mg/kg, during week 7 some males had thin appearance. At 500 mg/kg, during week 7 survivors appear thin. During weeks 7 -13, conditions of survivors improved. At 1000 mg/kg, during week 11, three males had sores on their dorsal area.

Clinical observations, females: Dose related signs of skin irritation were noted. At 250 mg/kg: During weeks 8-9, rough coats and thin appearance were reported. Conditions improved through the remainder of the study. At 500 mg/kg, in week 7, survivors appeared thin. Condition improved for the remainder of the study. At 1000 mg/kg from week 7, thin appearance and dermal effects were reported until the end of the study.

Mortality: 2m/3f @ 250; 4m/4f @ 500; 8m/4f @ 1000 mg/kg; most deaths occurred during weeks 6 - 8.

Microscopic findings: hyperkeratosis (minimal to moderate) in 14 mice, parakeratosis in 3 mice, and epithelial hyperplasia in 8 mice. Except for the tissue changes in the skin of treated mice, there were no tissue changes attributable to the effects of the test material in any of the treated mice examined.

Chronic Toxicity/Carcinogenicity:

NTP conducted a 2 year skin painting study in rats . Fifty animals per sex per dose were administered test material 5 days per week for 103 weeks. The applied doses were 0, 62.5 and 125 mg/kg in acetone with concentrations of 0, 3.75, 7.5% (adjusted based on body weight to allow for administration of 600 microliters).

The test material was a skin irritant and induced proliferative changes when applied topically. No consistent compound related reduction in body weight occurred in any of the treatment groups. Periodic weight fluctuations were attributed to problems with the automatic watering system. The Pathology Working Group which evaluated the study results concluded that 2-epoxyhexadecane in a two-year skin paint study did not produce any compound related neoplastic or systemic toxic lesions in F344 rats.

NTP conducted a similar 2 year skin painting study in mice . Fifty animals per sex per dose were administered test material 5 days per week for 103 weeks. The applied doses were 0, 62.5 and 125 mg/kg in acetone with concentrations adjusted based on body weight to allow for administration of 200 microliters.

All groups of male mice, including controls, had a high incidence of subcutaneous, mesenchymal neoplasms including malignant sarcoma, fibrosarcoma, neurofibrosarcoma, benign fibroma, with a combined incidence of 5 (10%), 8 (16%) and 13 (26%) in the control, low, and high dose groups. Only one fibrosarcoma was clearly identified as occurring at the application site. The tumors were all visible grossly.

There was a modest increase in the incidence of hepatocellular adenomas in all groups of male mice. The incidence of hepatocellular carcinoma was low in control male mice and average for treated animals.

The pathology working group concluded that 1,2-epoxyhexadecane in a two year skin painting study was associated with a dose-related increase in subcutaneous mesenchymal neoplasms in male B6C3F1 mice. A clear relationship between the location of the neoplasms and the area of skin exposure to the test compound cannnot be established from the data except for one tumor.

There were no other neoplastic or systemic toxic compound related effects in B6C3F1 mice. The pathology working group considered the modest increase in hepatocellular tumors in male mice not to be of biological significance.

These data are adequate to assess the repeated dose toxicity of tetradecyloxirane. No further testing is proposed.

5.4 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

For materials such as tetradecyloxirane, with limited exposure potential, the guidelines allow for reduced testing if there is adequate information from repeated dose studies for hazard assessment.

No information on the potential reproductive or developmental toxicity of tetradecyloxirane was located. However, there were no adverse histopathological findings in the reproductive tracts of rats or mice exposed dermally for 13 weeks or 2 years.

In addition to meeting the condition for reduced testing, there is supplementary information relevant to the material indicating that it would not be expected to affect reproductive performance or development of offspring.

The supplementary indications come from the available data for the higher olefins and their metabolism. Tetradecyloxirane is a metabolite of hexadecene. Hexadecene has been evaluated in the HPV program as part of the higher alpha olefins category of materials.

In vivo, hexadecene is metabolized to 1,2-dihydroxyhexadecane through a tetradecyloxirane intermediate. The conversion of tetradecyloxirane to 1,2-dihydroxyhexadecane is dependent upon epoxide hydrolase. Based on the information from the alpha-olefins category, no reproductive or developmental effects are anticipated. Since tetradecyloxirane is the reactive metabolite, the evalaution of hexadecene is relevant since the ultimate metabolite is the same for both compounds. The materials tested in the alpha-olefins category did not elicit reproductive or developmental effects at doses up to 1000 mg/kg in rats.

In addition, there is information on higher mmolecular weight analogies and materials with higher degrees of epoxidation, eg, epoxidized oils. As in the case of the alpha-olefins, they did

not elicit any reproductive or developmental effects in rats at doses up to 1000 mg/kg. Based on the lack of effects in structurally similar materials of lower and higher molecular weight, and, degree of epoxidation, there is adequate information upon which to base a screening level hazard assessment for these endpoints.

Because the material is an intermediate with limited transport and supplementary data are available regarding reproductive and developmental effects, no further testing is proposed.

6 GENETIC TOXICITY

Data from various *in vitro* gene mutation and chromosomal aberration tests of tetradecyloxirane were obtained from company-sponsored studies or from the scientific literature. *In vitro* genetic toxicity data are summarized in Table 4.

Table 4. *In Vitro* Mutagenicity and Genotoxicity of Tin Tetrachloride

Endpoint	Results	Source
Bacterial reverse mutation assay (single strain and multiple strains)	Negative	Hengler, W.C., Slesinski, R.S. and Frank, F.R. (1984); Canter et al., 1986.
Mouse lymphoma assay	Positive	McGregor DB, et al., 1988.
Sister Chromatid Exchange Assay (Chinese hamster cells)	Negative	von der Hude et al., 1991, Slesinski, et al., 1984 Union Carbide Corporation, 1984

There are adequate data to assess genotoxicity. No further testing is proposed.

7 REFERENCES

Canter DA, et al. Comparative Mutagenicity of Aliphatic Epoxides in Salmonella. Mutat Res 172(2):105-138, 1986

Deneer JW Sinnige TL Seinen W Hermens JL A Quantitative Structure-Activity Relationship For The Acute Toxicity Of Some Epoxy Compounds To The Guppy. Aquat Toxicol., 13: 195-204, 1988

Dow Europe GMBH MSDS alpha-Olefin Epoxide C-16, 30/3/04
EPI Suite v3.12, US EPA
Hengler, W.C., Slesinski, R.S. and Frank, F.R. (1984). Alpha-Olefin Epoxide C-16 Salmonella/Microsome (Ames) bacterial mutagenicity assay.
McGregor DB, et al. Responses of the L5178Y TK+/TK- Mouse Lymphoma Cell Forward Mutation Assay: III. 72 Coded Chemicals. Environ Mol Mutagen 12(1):85-154, 1988.

Myers, R.C. and Christopher, S.M. (1992). .... cutaneous and ocular irritancy testing using the rabbit.
US National Toxicology Program (NTP) Unpublished study (C55538) summarized by Tracor-Jitco, Inc., Subchronic Test Of 1,2-Epoxyhexdecane (C55538) In B6C3F1 Mice And Fisher 344 Rats By Dermal Application, EPA/OTS DOC 40-8077013 NTIS/OTS0508872

Nycum, J.S. (1968). Single dose toxicity and irritation studies on Epoxides
Safety and Toxicity Data prepared for 1,2-epoxyhexadecane by Tracor Jitco July 26, 1978.
Slesinski, R.S. and Frank, F.R. (1984). a-Olefin Epoxide -16 in vitro Genotoxicity Studies: Sister Chromatid Echange Test.
SPRINGBORN ENVIRONMENTAL SCIENCES Acute Oral Toxicity Study in Rats with Vikolox 16, SLI STUDY NO. 3255.80, 19 August 1996.
SPRINGBORN ENVIRONMENTAL SCIENCES Dermal Sensitization Study in Guinea Pigs with Vikolox 16, SLI STUDY NO. 255.84, 10 Sept 1996.
SPRINGBORN ENVIRONMENTAL SCIENCES, Primary Skin Irritation Study in Rabbits with Vikolox 16, SLI STUDY NO. 255.83 19 August 1996.
SPRINGBORN ENVIRONMENTAL SCIENCES. Acute dermal toxicity study in rats with Vikolox 16, SLI STUDY NO. 3255.81, 19 August 1996.
SPRINGBORN ENVIRONMENTAL SCIENCES. Primary Eye Irritation Study in Rabbits with Vikolox 16, SLI STUDY NO. 255.82, 19 August 1996.
The Dictionary of Substances and Their Effects (DOSE, 3rd Electronic Edition) 2005 by The Royal Society of Chemistry/Knovel Corp.
Union Carbide Corporation. Alpha-Olefin Epoxide C-16 Salmonella/Microsome (Ames) Bacterial Mutagenicity Assay With Cover Letter. TSCA 8(d) submission. TSCATS Microfiche No. 206602. 03/05/84.

von der Hude W, Carstensen S, Obe G, Structure-Activity Relationships Of Epoxides: Induction Of Sister-Chromatid Exchanges In Chinese Hamster V79 Cells, Mutat Res, 249: 55-70,1991.

Wood WP, Properties Of Alkyl-Epoxides - Table I With Cover Letter, US Environmental Protection Agency EPA/OTS DOC 40-8277016, NTIS/OTS0508875